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Force traction microscopy: An inverse problem with pointwise observations

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ABSTRACT

Force traction microscopy is an inversion method that allows one to obtain the stress field applied by a living cell on the environment on the basis of a pointwise knowledge of the displacement produced by the cell itself. This classical biophysical problem, usually addressed in terms of Green functions, can be alternatively tackled using a variational framework and then a finite elements discretization. In such a case, a variation of the error functional under suitable regularization is operated in view of its minimization. This setting naturally suggests the introduction of a new equation, based on the adjoint operator of the elasticity problem. In this paper we illustrate the rigorous theory of the two-dimensional and three-dimensional problems, involving in the former case a distributed control and in the latter case a surface control. The pointwise observations require one to exploit the theory of elasticity extended to forcing terms that are Borel measures.

0. Introduction

Many living cells have the ability to migrate, both in physiological and pathological conditions; examples include those of wound healing, embryonic morphogenesis and the formation of new vessels in tumors. The motility of a cell is driven by the reorganization of its inner structure, the cytoskeleton, according to a complex machinery. The net effect of this process is that a cell is able to apply a stress on the environment, pulling the surrounding material and produce its own movement. The biophysical details of the internal engine of a cell are far from being fully understood or rephrased in terms of a mathematical model; nevertheless its inverse counterpart, that is the determination of forces on the basis of measured displacement, is quite a popular problem in the biophysical community.

The early idea of studying the force applied by cells in their migration as an inverse problem dates back to the work of Harris and co-workers in the eighties [1]. They considered the action of fibroblasts (cells with a high degree of contractility) laying on a flat polyethylene sheet. They argued that the wrinkles produced by the cells on the substrate are a good indicator of the stress exerted by the cells on the surface itself: the direction, and height and length of the buckles correlate with the direction and intensity of the force, respectively.

After several efforts, the correct methodology for translating the qualitative argument above into a quantitative procedure was formulated about twenty years later in a seminal paper by Dembo et al. [2], under the assumption of two-dimensional height-averaged strain, and then generalized to a full three-dimensional setting by Dembo and Wang [3]. Their technique was new, both in a technological and in a methodological sense. The use of a soft polyacrylamide substrate avoids the emergence of wrinkles, that are typically produced in a nonlinear elasticity range. Thus restricting to a linear elastic

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regime, the displacement of fluorescent beads dispersed in the elastic material is evaluated from different images. Finally, they solve the direct problem in terms of Green elasticity functions and then minimize the error under regularization by a discrete Tikhonov method. This method has become a standard in biophysics and has been applied to a variety of cell types in a number of experimental settings in order to investigate cell adhesion, contractility, variability of the dynamics of stiffer and softer substrates, the response to chemotactic stimuli and many other phenomena.

Inverse problems in elasticity have been tackled in a variational framework in several works [4,5]. The usual questions addressed in the literature reflect classical problems of mechanics (in particular geomechanics) such as the determination of elastic moduli or the identification of cavities in the material. Biophysics here offers new questions in data inversion: the ability of the living matter (such as a living cell) to actively produce forces naturally leads to the problem of determining the pattern of such a stress field. This question is not traditional in engineering practice.

The force traction microscopy described by Dembo et al. [2] has been addressed in a continuous variational framework in a past work [6]. Again, the starting point is a Tikhonov functional defined as the error norm plus a penalization of the magnitude of the force. If a variation of the cost functional is operated at a continuous level, the definition of an adjoint problem for the unknown force naturally arises. In this way, two elliptic partial differential equations coupled by the (linear) source terms are obtained and their approximate solution can be addressed by means of, for instance, a finite element discretization. The adjoint method has been applied to evaluate the surface tension generated by different cell lines, solving a set of equations for the two-dimensional depth-averaged elasticity.

Although the optimal control approach is less popular than the standard inverse method based on Green functions, it has some attractive features that make it worth to investigate further. The first reason is of numerical type: a variational formulation, based on the forward and adjoint problem to be solved jointly, can be addressed by using a finite element code where local approximating polynomials might be computationally more efficient than convolution of global Green functions plus a decoupled minimizing algorithm. The second, more relevant, issue is that Green functions of the elasticity problem are known explicitly only for a few simple geometrical configurations, including the infinite half-plane. The typical biological domain where cells apply stress in their three-dimensional migration is geometrically complex and Green functions are not known a priori. Last but not least, the optimum control theory offers a framework for a natural generalization of the forward model to a number of important biological characterizations, in particular nonlinear elastic materials, possibly including non-homogeneities and anisotropy due to fibers embedded in the material itself.

The aim of this paper is to state firm theoretical grounds for the formal derivation and the rigorous theory of the force traction microscopy in three dimensions. Such a theory is, to our knowledge, still lacking and this paper aims to fill this gap. The availability of pointwise observations makes it impossible to state the well posedness of the problem using Hilbert spaces only and we resort to the theory developed by Casas [7–9]. Existence and uniqueness of the solution are proved in a general context that encompasses distributed boundary control in two and three dimensions. The differential systems determined and analyzed in this work constitute the intermediate mathematical step in view of the numerical discretization and applications to applied biophysical questions in cell motility.

1. Background

In this section we summarize a number of classical results of functional analysis and partial differential equations that will be used in this paper.

1.1. Functional spaces

The theory of linear elliptic equations is classically based on the definition of some suitable functional spaces. We sketch here below the main definitions and properties; more details can be found, for instance, in [10,11].[1]

Definition 1. Given Ω, an open set in $\mathbb{R}^n$, we set up the following Sobolev spaces:

- $L^p(\Omega) := \{\mathbf{u} : \Omega \to \mathbb{R}^m \mid \int_\Omega |\mathbf{u}|^p < \infty\}$;
- $W^{k,p}(\Omega) := \{\mathbf{u} \in L^p(\Omega) \mid \nabla^i \mathbf{u} \in L^p(\Omega),\ \forall i \in \{1, \ldots, k\}\}$.

Here ∇^i is the ith gradient and $\nabla^0 := \mathbf{1}$ is the identity tensor.

Non-integer indexed Sobolev spaces (i.e. when $k \in \mathbb{R}$) can also be defined (see [12]), and they will turn out to be useful in the following. Relevant examples of Sobolev spaces include the following Hilbert spaces:

- $L^2(\Omega)$ with the scalar product $(\mathbf{u}|\mathbf{v})_{L^2(\Omega)} := \int_\Omega \mathbf{u} \cdot \mathbf{v}$;
- $H^k(\Omega) := W^{k,2}(\Omega)$ with the scalar product $(\mathbf{u}|\mathbf{v})_{H^k(\Omega)} := \sum_{i=0}^k \int_\Omega \nabla^i \mathbf{u} \cdot \nabla^i \mathbf{v}$.

[1] In this work we tacitly assume that we are dealing with domains enjoying some special properties. The interested reader may find in [10,11] the hypothesis needed to develop the theory. In the following sections, we will stick with bounded C^2-regular boundary, which is enough to prove the results shown here.

The trace operator $\tau_{\partial\Omega}$ is defined as the restriction of a function defined on $\Omega \subset \mathbb{R}^n$ over its boundary $\partial\Omega$, having dimension $n-1$. Traces are characterized by the following [10,12]:

Theorem 2 (*Trace Theorem*)**.** *Let $\Omega \in \mathbb{R}^n$ an open bounded set with boundary $\partial\Omega$. The trace $\tau_{\partial\Omega}$ is a linear and continuous functional such that:*

- *$W^{1,p}(\Omega)$ is injected into $L^p(\partial\Omega)$ if $p < n$;*
- *if $\mathbf{u} \in H^k(\Omega)$ then $\tau(\nabla^i \mathbf{u}) \in H^{k-1/2}(\partial\Omega)$.*

Using traces, we can define subspaces of Sobolev spaces that allow us to treat boundary conditions. Let us define the space of fields in $H^1(\Omega)$ satisfying a homogeneous Dirichlet boundary condition on Γ_D:

$$H^1_{0,\Gamma_D}(\Omega) := H^1(\Omega) \cap \ker(\tau_{\Gamma_D}).$$

A similar construction allows us to define, more generally, the space $W^{1,s}_{0,\Gamma_D}$ $(s > 0)$; see [10,11]. It is worth noting that (thanks to the Poincaré Lemma [13]) $H^1_{0,\Gamma_D}(\Omega)$ can be equipped with a scalar product, $(\mathbf{u}|\mathbf{v})_{H^1_{0,\Gamma_D}(\Omega)} := \int_\Omega \nabla\mathbf{u} \cdot \nabla\mathbf{v}$, equivalent to the one given above.

The following special case of the Sobolev Embedding Theorem [11] holds:

Theorem 3. *Let $\Omega \subset \mathbb{R}^n$ be an open bounded domain $n = 2, 3$. Then:*

- *$W^{1,p}(\Omega) \hookrightarrow C^0(\mathrm{cl}\,\Omega)$, $p > n$;*
- *$H^2(\Omega) \hookrightarrow W^{1,p}(\Omega)$, $p \in [1, \frac{2n}{n-2}]$;*
- *$W^{1,p}(\Omega) \hookrightarrow L^2(\Omega)$, $p \geq \frac{2n}{n+2}$;*

where $\hookrightarrow$ means that the inclusion is continuous and the symbol cl *denotes the closure of a set.*

1.2. Linear elasticity

In a spatial description of continuum mechanics the force balance equations on a bounded domain $\Omega \subset \mathbb{R}^n$ $(n \leq 3)$ read[2]:

$$\begin{cases} -\nabla \cdot \mathbf{T} = \mathbf{b}, & \text{in } \Omega, \\ \mathbf{Tn} = \mathbf{c}, & \text{on } \Gamma_N, \\ \mathbf{u} = 0, & \text{on } \Gamma_D. \end{cases} \tag{1}$$

where $\Gamma_D, \Gamma_N \subset \partial\Omega$ are open sets such that $\mathrm{cl}(\Gamma_N \cap \Gamma_D) = \emptyset$ and $\Gamma_N \cup \Gamma_D = \partial\Omega$. In our framework the domain Ω is the portion of the space occupied by the elastic gel. Its boundary $\partial\Omega$ can be constrained not to move (zero displacement on Γ_D) or can be loaded by the action of the cell on Γ_N. The vector fields $\mathbf{b}$ and $\mathbf{c}$ are the given applied load per unit volume and surface, respectively; they represent the traction exerted by the cell on the gel.

The symbol $\mathbf{T} : \mathbf{x} \in \Omega \mapsto \mathbf{T}(\mathbf{x}) \in \mathrm{Sym}(\mathbb{R}^n)$ denotes the Cauchy stress tensor field of the material contained in Ω. The internal forces in an elastic body depend on the strain of the material with respect to a reference relaxed configuration. If we denote by $\mathbf{u} : \mathbf{x} \in \Omega \mapsto \mathbf{u}(\mathbf{x}) \in \mathbb{R}^n$ the displacement field due to the traction of the cell, we must have $\mathbf{T} = \hat{\mathbf{T}}(\nabla\mathbf{u})$, $\hat{\mathbf{T}}$ being the constitutive map for $\mathbf{T}$. For arguments of objectivity, such a constitutive map must be nonlinear [14]. For small deformations, the stress tensor $\mathbf{T}$ can be approximated by its first-order derivative evaluated in the relaxed configuration: $\mathbf{T} = \hat{\mathbf{T}}(\nabla\mathbf{u}) \approx \hat{\mathbf{T}}'(0)[\nabla\mathbf{u}]$. Here $\hat{\mathbf{T}}'(0) := \mathbb{C}$ is a fourth-order constant tensor: in index form, $T_{ij} = C_{ijmn}\,\partial_n u_m$.

Therefore $\mathbb{C} \in \mathrm{Lin}(\mathrm{Lin}(\mathbb{R}^n))$ and it satisfies the following conditions [14]:

$$\mathbb{C}[\mathbf{S}] = \mathbb{C}[\mathbf{S}^T], \quad \forall \mathbf{S} \in \mathrm{Lin}(\mathbb{R}^n), \tag{2}$$

$$\mathbf{S} \cdot \mathbb{C}[\mathbf{S}] \geq \alpha \mathbf{S} \cdot \mathbf{S}, \quad \alpha > 0,\ \forall \mathbf{S} \in \mathrm{Sym}(\mathbb{R}^n), \tag{3}$$

$$\mathbf{S} \cdot \mathbb{C}[\mathbf{H}] = \mathbf{H} \cdot \mathbb{C}[\mathbf{S}], \quad \forall \mathbf{H},\ \mathbf{S} \in \mathrm{Sym}(\mathbb{R}^n). \tag{4}$$

The condition (2) accounts for the objectivity in the linearized case, the symmetry property (4) reflects the torque balance while the inequality (3) is a requirement of "stability", namely strong ellipticity in the partial differential equation literature.

The variational form of (1) in the case of linear(ized) elasticity is, formally,

$$\int_\Omega \mathbb{C}[\nabla\mathbf{u}] \cdot \nabla\mathbf{v} = \int_\Omega \mathbf{b} \cdot \mathbf{v} + \int_{\Gamma_N} \mathbf{c} \cdot \mathbf{v}, \tag{5}$$

for all suitable $\mathbf{v}$. The problem (1) has been studied in great detail [14,15]. Several results of well posedness and regularity are known and we summarize here only those strictly needed for our purposes.

[2] Vectors (here elements of $\mathbb{R}^n$) are indicated with boldface italic letters, second-order tensors (here elements of $\mathrm{Lin}(\mathbb{R}^n)$) with capital boldface letters and fourth-order tensors (here elements of $\mathrm{Lin}(\mathrm{Lin}(\mathbb{R}^n))$) with capital blackboard boldface. Scalar products in these spaces are indicated with the same symbol "·", the context clarifying the meaning.

First of all, the following holds:

Theorem 4 (*The Lax–Milgram Lemma*)**.** *Given the problem in (5) with $\mathbf{b} \in L^2(\Omega)$, $\mathbf{c} \in L^2(\Gamma_N)$, Ω a bounded open set with Lipschitz boundary and $\Gamma_D \neq \emptyset$, let the coefficient $\mathbb{C}$ satisfy conditions (3) and (4); then, problem (5) admits a unique solution in $H^1_{0,\Gamma_D}(\Omega)$ which depends continuously on the data.*

In the following we assume that we are dealing with a bounded, open domain Ω with smooth enough boundary $\partial\Omega$ (C^2-regularity is enough). The weak solution of an elliptic problem possesses remarkable regularity properties [14,16]:

Theorem 5. *Let the problem (5) be given with $\mathbf{b} \in L^2(\Omega)$, $\mathbf{c} \in H^{\frac{1}{2}}(\Gamma_N)$ and Ω a bounded open set such that its boundary $\partial\Omega$ is C^2-regular. If $\Gamma_D \neq \emptyset$ and $\Gamma_N = \emptyset$ or $\mathrm{cl}(\Gamma_N \cap \Gamma_D) = \emptyset$ then the solution $\mathbf{u}$ of (5) belongs to $H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$ and depends continuously on the data.*

According to Theorems 3 and 5, the solution of an elliptic problem is continuous when the above hypothesis holds.

For reasons that will be clear in the following, we need to extend the above theory to the case of forcing terms of the linear elasticity operator that are Borel measures (i.e. elements of the dual space of C^0; see [17]). Following Casas [9,8], the following theorem holds for the pure Dirichlet and pure Neumann cases, although a generalization to the mixed case is straightforward when Ω is sufficiently regular:

Theorem 6. *Let Ω a bounded open set such that its boundary $\partial\Omega$ is C^2-regular. Set $s \in [1, \frac{n}{n-1})$ and s' such that $\frac{1}{s} + \frac{1}{s'} = 1$. Then, the following variational problem: find $\mathbf{u} \in W^{1,s}(\Omega)$ such that $\forall \mathbf{v} \in W^{1,s'}(\Omega)$ Eq. (5) holds, given $\mathbf{b}$ and $\mathbf{c}$ regular Borel measures, admits a unique solution which depends continuously on the data.*

1.3. Optimal control

In this work, the term on the right hand side of Eq. (5) is to be interpreted as a control, so the traction at the boundary $\mathbf{c}$ or the volume force $\mathbf{b}$ is formally an unknown of the problem. In the following, such a control will be generically indicated as $\mathbf{f} \in \mathsf{F}$, where F is a suitable Hilbert space. We also denote by U the Hilbert space that the displacement $\mathbf{u}$ belongs to.

We introduce below two operators that will turn out to be useful for the applications to be discussed in the following.

Solution operator: We define the solution operator $\mathcal{S} : \mathsf{F} \to \mathsf{U}$, the map that, for a given control $\mathbf{f}$ on the right hand side of (1) or (5), assigns the displacement field $\mathbf{u}$ that solves the problem. More specifically, we study the following two cases[3]:

- distributed control: $\mathcal{S}\mathbf{b} = \mathbf{u}$ iff (1) or (5) holds, with $\mathbf{c} = 0$;
- boundary control: $\mathcal{S}\mathbf{c} = \mathbf{u}$ iff (1) or (5) holds, with $\mathbf{b} = 0$.

In this section we assume that F and U are tuned in such a way that

$$\mathcal{S} \in \mathrm{Lin}(\mathsf{F}, \mathsf{U}). \tag{6}$$

The rigorous proof of this fact in the specific cases of interest herein is given in Sections 2 and 3.

Observation operator: In this work we are interested in pointwise observation of the state. Typically, in cellular traction microscopy some beads are seeded into the elastic Matrigel and their displacement is recorded during the motion of the cell. Mathematically, the observation operator is therefore a list of Dirac delta distributions, i.e. $\mathcal{O} := (\delta_{\mathbf{x}_1}, \ldots, \delta_{\mathbf{x}_N})$. It can be easily shown that this operator is continuous in the functional spaces of interest to us if $\Omega \subset \mathbb{R}^n$, $n \leq 3$. In fact (see [17]):

Proposition 7. *$\mathcal{O}$ is a linear and continuous form on $C^0(\mathrm{cl}\,\Omega)$ if $\Omega \subset \mathbb{R}^n$ ($n = 1, 2, 3$).*

Under suitable regularity of the control $\mathbf{f}$, in the following section we will prove that

$$\mathcal{O} \in \mathrm{Lin}(\mathsf{U}, \mathbb{R}^{Nn}). \tag{7}$$

1.3.1. The penalty functional

The information provided experimentally for solving the inverse problem, i.e. the pointwise measurements of the state $\mathbf{u} \in \mathsf{U}$, is usually not sufficient for ensuring the well posedness of Problem (1). The problem is therefore underdetermined and, as is customary, we state a suitable minimization problem to circumvent this drawback. Let:

- $\mathbf{f} \in \mathsf{F}_{\mathrm{adm}}$, where $\mathsf{F}_{\mathrm{adm}}$ is a closed subspace of F;
- $\mathsf{X} := \mathbb{R}^{Nn}$, where N is the number of beads and $n = 1, 2, 3$ as before (we denote with the circle $\circ$ the scalar product in X);
- $\mathcal{S} \in \mathrm{Lin}(\mathsf{F}, \mathsf{U})$ is the solution control-to-state map defined previously, satisfying (6);
- $\mathcal{O} \in \mathrm{Lin}(\mathsf{U}, \mathsf{X})$ is the observation operator defined above, satisfying (7);

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3 For simplicity, we restrict ourselves to the case where only the control appears as a forcing term. The more general case in which the forces in (1) or in (5) are sums of known fields and the control is analogous but technically more onerous, since the solution operator $\mathcal{S}$ is affine (see [18]).

- $u_0 = (\mathbf{u}_0^1, \ldots, \mathbf{u}_0^N) \in \mathsf{X}$ is the list of the measured displacements, supposed to be known;
- $\varepsilon > 0$ is the penalization parameter, to be fixed.

Definition 8. The penalty functional $\mathcal{J} : \mathsf{F} \to \mathbb{R}^+$ is defined as

$$\mathcal{J}(\mathbf{g}) = \frac{1}{2}\|\mathcal{O}\mathcal{S}\mathbf{g} - u_0\|_{\mathsf{X}}^2 + \frac{\varepsilon}{2}\|\mathbf{g}\|_{\mathsf{F}}^2. \tag{8}$$

Our goal is to minimize the functional $\mathcal{J}$ on $\mathsf{F}_{\mathrm{adm}}$. If the forward problem (1) has the properties stated in the previous section, the existence and uniqueness of a global minimum for the functional $\mathcal{J}$ above can be readily obtained. We first state (see [18]):

Proposition 9. *The penalty functional $\mathcal{J}$ in (8) is coercive and strictly convex. Moreover, if (6) and (7) hold, it is also continuous.*

Then, we recall a classical theorem [18]:

Theorem 10. *Let $\mathcal{J} : \mathsf{F}_{\mathrm{adm}} \subset \mathsf{F} \to \mathbb{R}^+$ be a continuous, coercive and strictly convex functional. If $\mathsf{F}_{\mathrm{adm}}$ is a closed subspace of F then a unique minimum point of $\mathcal{J}$ exists.*

After proving that $\mathcal{J}$ admits a unique minimum point, say $\mathbf{f}$, we can characterize it using the Euler equation associated with $\mathcal{J}$. It is easy to show that:

Proposition 11. *If (6) and (7) hold, then $\mathcal{J}$ is differentiable.*

The following statement summarizes the results obtained in this section:

Theorem 12. *Let F be a Hilbert space, with $\mathcal{J} : \mathsf{F}_{\mathrm{adm}} \subset \mathsf{F} \to \mathbb{R}^+$ defined as in (8) and $\mathsf{F}_{\mathrm{adm}}$ a closed subspace of F. Let the hypotheses (6) and (7) for $\mathcal{S}$ and $\mathcal{O}$ hold.*

Then, a unique minimum point of $\mathcal{J}$ exists, say $\mathbf{f} \in \mathsf{F}_{\mathrm{adm}}$, and it solves

$$\mathcal{P}\mathcal{J}'(\mathbf{g}) = 0 \tag{9}$$

where the prime (′) means differentiation and $\mathcal{P} \in \mathsf{Lin}(\mathsf{F})$ is the projection onto $\mathsf{F}_{\mathrm{adm}}$.

1.3.2. The adjoint state

Since the functional $\mathcal{J}$ admits a unique global minimum in a closed subspace $\mathsf{F}_{\mathrm{adm}} \subset \mathsf{F}$ and is differentiable, from (9) it follows that the optimal control $\mathbf{f} \in \mathsf{F}_{\mathrm{adm}}$ satisfies

$$\mathcal{P}\mathcal{J}'(\mathbf{f}) = 0 \Leftrightarrow \varepsilon\mathbf{f} + \mathcal{P}(\mathcal{O}\mathcal{S})^T(\mathcal{O}\mathcal{S}\mathbf{f} - u_0) = 0. \tag{10}$$

To avoid the evaluation of the operator $\mathcal{S}$ in Eq. (10), we introduce the so called adjoint state [18]. The proof of well posedness of the following problem will be given in the following sections for the specific contexts. Let $\mathbf{p} \in \mathsf{P}$ be formally defined as

$$\mathcal{A}^T\mathbf{p} = \mathcal{O}^T(\mathcal{O}\mathbf{u} - u_0), \tag{11}$$

where P is a suitable functional space and $\mathcal{A}^T : \mathsf{P} \to \mathsf{U}^*$ is an operator to be assigned. Roughly speaking, $\mathcal{A}$ should be taken such that the operator $\mathcal{S}\mathcal{A}$ will be easy to deal with. For example, in Section 2, we will find that $\mathcal{S}\mathcal{A}$ is the identity map. In contrast to most of the literature on the subject (e.g. [18]), our work strictly requires a distinction between $\mathcal{A}$ and $\mathcal{S}^{-1}$ as we shall see in Section 3. Now, plugging Eq. (11) into (10) we obtain

$$\varepsilon\mathbf{f} + \mathcal{P}(\mathcal{A}\mathcal{S})^T\mathbf{p} = 0. \tag{12}$$

The choice of the operator $\mathcal{A}$ and the analysis of its continuity property are the main goals of the paper. We deal with this issue in the following section, discussing the control of Dirichlet and mixed problems.

1.4. Optimal control and inverse problems

Since we want to use the tool presented above as an inverse method rather than an optimal control one, it is worthwhile to recall some basic definitions and properties of inverse and ill-posed problems and their regularization. As a basic reference for this theory we refer the reader to [19]. Here the discussion is kept at a minimum degree of complexity and, hence, of rigor. Let us focus on our basic problem, i.e. find the force producing exactly the displacement measured which is written in the following formulas:

$$\text{find } \mathbf{f} \in \mathsf{F}_{\mathrm{adm}} \quad \text{such that } \mathcal{O}\mathcal{S}\mathbf{f} = u_0. \tag{13}$$

Since the problem above can in principle fail to meet one or more of the three Hadamard conditions of well posedness (and actually does, in practice), it is convenient to introduce a mollified notion of a solution. We call $\mathbf{f}_{\mathrm{BAS}} \in \mathsf{F}_{\mathrm{adm}}$ the *best* *approximation solution* of (13) if

$$\mathbf{f}_{\mathrm{BAS}} = \arg\min_{\mathsf{F}_{\mathrm{adm}}}\{\|\mathbf{g}\|_{\mathsf{F}} \text{ such that } \mathbf{g} = \arg\min_{\mathsf{F}_{\mathrm{adm}}}(\mathbf{h} \mapsto |\mathcal{O}\mathcal{S}\mathbf{h} - u_0|)\}. \tag{14}$$

This definition naturally induces a weakened concept of the inverse map of $\mathcal{O}\mathcal{S}$, namely the *Moore–Penrose Generalized Inverse*, $(\mathcal{O}\mathcal{S})^{\dagger}$. Avoiding technical definitions, we can recall its most interesting properties:

$$\mathrm{dom}(\mathcal{O}\mathcal{S})^{\dagger} := \mathrm{ran}(\mathcal{O}\mathcal{S}) + (\mathrm{ran}(\mathcal{O}\mathcal{S}))^{\perp} \tag{15}$$

$$(\mathcal{O}\mathcal{S})^{\dagger} : u_0 \in \mathbb{R}^n \mapsto \mathbf{f}_{\mathrm{BAS}} \in \mathsf{F}_{\mathrm{adm}} \tag{16}$$

Since the range of the operator $\mathcal{O}\mathcal{S}$ ($\mathrm{ran}(\mathcal{O}\mathcal{S})$) is a subspace of $\mathbb{R}^{3N}$, we can apply Proposition 2.4 and Theorem 2.5 of [19], saying that the above defined $\mathbf{f}_{\mathrm{BAS}}$ exists uniquely and the operator $(\mathcal{O}\mathcal{S})^{\dagger}$ is continuous.

Applying the Tikhonov regularization procedure to the operator $(\mathcal{O}\mathcal{S})^{\dagger}$, we end up with the minimum problem for the family, with respect to the parameter ε, of the penalty functional in (8). Actually, Theorem 5.2 in [19] confirms that the sequence of minima of $\mathcal{J}$ converges strongly to $\mathbf{f}_{\mathrm{BAS}}$ provided the regularization parameter ε and the noise level for the data u_0 tend to 0 in a suitable way.

2. The Dirichlet problem with distributed control

In this section we introduce and analyze an inverse problem which arises in cellular traction microscopy on flat substrates. We provide well posedness results for the problem formally stated in [6,20] in the plane. The results still hold for a Dirichlet problem in $\mathbb{R}^3$ with almost no modifications.

2.1. The forward problem

Let $\Omega \subset \mathbb{R}^2$ be an open bounded domain with C^2-regular border, where the Dirichlet problem of linear elasticity applies. For this section we consider $\Gamma_D = \partial\Omega$, $\mathsf{F} = L^2(\Omega)$, $\mathsf{U} = H^2(\Omega) \cap H^1_0(\Omega)$, $\mathbf{c} = 0$ and $\mathbf{b} := \mathbf{f}$. The problem (1) or (5) with the above hypothesis reads as follows:

$$\text{given } \mathbf{f} \in L^2(\Omega), \text{ find } \mathbf{u} \in H^2 \cap H^1_0(\Omega) \text{ s.t. } \forall \mathbf{v} \in H^1_0(\Omega) :$$

$$\int_{\Omega} \nabla\mathbf{u} \cdot \mathbb{C}[\nabla\mathbf{v}] = \int_{\Omega} \mathbf{f} \cdot \mathbf{v}. \tag{17}$$

According to the notation introduced in the previous section, if $\mathbf{u}$ and $\mathbf{f}$ satisfy (17), then we say that $\mathcal{S}\mathbf{f} = \mathbf{u}$. If $\mathbf{f} \in L^2(\Omega)$ is known, the problem (17) is well posed from Theorem 4 and its solution satisfies, thanks to Theorem 5,

$$\|\mathcal{S}\mathbf{f}\|_{H^2(\Omega)} \le k\|\mathbf{f}\|_{L^2(\Omega)}, \quad k > 0, \tag{18}$$

which is the continuity estimate required in (6) for the solution operator.

2.1.1. The admissible force space

Let $\Omega_c \subset \Omega$ be the Lebesgue-measurable set where the cell lies and $\mathbf{f} \in \mathsf{F} = L^2(\Omega)$ the force density per unit surface exerted by the cell. Since neither external forces nor constraints apply on the cell and the inertia is negligible, we can argue that its force field $\mathbf{f}$ must have null average and null average momentum, so it belongs to[4]:

$$\mathsf{F}_{\mathrm{adm}} := \left\{ \mathbf{g} \in \mathsf{F} = L^2(\Omega) \,\middle|\, \int_{\Omega_c} \mathbf{f} = 0, \ \int_{\Omega_c} \mathbf{r} \times \mathbf{f} = 0, \ \mathbf{f} = 0 \text{ a.e. on } \Omega \setminus \Omega_c \right\}. \tag{19}$$

We can easily prove the following characterization of $\mathsf{F}_{\mathrm{adm}}$.

Proposition 13. $\mathsf{F}_{\mathrm{adm}}$, *as defined in* (19), *is a closed subspace of* F.

2.2. Optimal control

2.2.1. The penalty functional

Our goal is to determine $\mathbf{f}$ which minimizes the penalty functional in (8) and belongs to a closed subspace $\mathsf{F}_{\mathrm{adm}} \subset \mathsf{F}$. In the previous sections, we have proved (see inequality (18)) that the suitable choice of U and F made at the beginning of this section yields a continuous solution operator $\mathcal{S}$ (i.e. satisfying (6)). Since the solution $\mathbf{u}$ belongs to $H^2(\Omega)$, the observation map $\mathcal{O}$ is also continuous. In fact, by the Sobolev Embedding Theorem, Theorem 3, $H^2(\Omega) \hookrightarrow C^0(\mathrm{cl}\,\Omega)$ when $n = 2, 3$ and, thanks to Proposition 7, the condition (7) is clearly satisfied. We can then apply Theorem 12 and find that, in this case, our functional $\mathcal{J}$ admits a unique minimum point and it is differentiable therein.

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[4] To define the wedge product in $\mathbb{R}^2$, we proceed in this way. Fix $\mathbf{J} \in \mathrm{Skw}(\mathbb{R}^2) \cap \mathrm{Ort}(\mathbb{R}^2)$ as one of the two rotation wises in $\mathbb{R}^2$ [21]. Define $\mathbf{h} \times \mathbf{g} = \mathbf{J}\mathbf{h} \cdot \mathbf{g}$ for all vectors $\mathbf{g}$, $\mathbf{h}$ of $\mathbb{R}^2$.

Moreover we have defined $\mathbf{r}(\mathbf{x}) := \mathbf{x} - \mathbf{o}$ where $\mathbf{o} \in \mathbb{R}^3$ is a given point.

2.2.2. The adjoint state

In this section we explicitly assign the operator $\mathcal{A}$ appearing, in abstract form, in Eq. (11) and we prove some of its properties. Taking $\mathcal{A} = \mathcal{S}^{-1}$, we argue that Problem (11) can be rewritten as follows (cf. [7])[5]:

$$\text{find } \mathbf{p} \in W_0^{1,s}(\Omega) \text{ s.t. } \forall \mathbf{q} \in W_0^{1,s'}(\Omega):$$
$$\int_\Omega \nabla \mathbf{p} \cdot \mathbb{C}[\nabla \mathbf{q}] = (\mathcal{O}\mathbf{u} - u_0) \circ \mathcal{O}\mathbf{q}. \tag{20}$$

The next step is to prove the well posedness of the above equation.

Proposition 14. *The problem in (20) is well posed when $s \in [1, \frac{n}{n-1})$, s' is conjugate with s, Ω is a bounded domain with C^2-boundary and $n = 2, 3$.*

Proof. As a consequence of Proposition 7, $\mathcal{O}^T(\mathcal{O}\mathbf{u} - u_0)$ is a Borel measure (having fixed $\mathbf{u} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega) \hookrightarrow C^0(\mathrm{cl}\,\Omega)$ as noted before).

We also observe that, by the Sobolev Embedding Theorem:

$$\mathbf{q} \in W^{1,s'}(\Omega) \hookrightarrow C^0(\mathrm{cl}\,\Omega) \quad \text{if } s' > n \Leftrightarrow s \in \left[1, \frac{n}{n-1}\right).$$

Then, we can apply Theorem 6 with $s \in [1, \frac{n}{n-1})$ and $n = 2, 3$ to prove the thesis. □

Using Sobolev Embedding Theorem, Theorem 3, it can be proved that

$$\mathbf{p} \in W^{1,s}(\Omega) \hookrightarrow L^2(\Omega) \quad \text{if } s \geq \frac{2n}{n+2} \Leftrightarrow s' \in \left[1, \frac{2n}{n-2}\right).$$

Moreover, let $\mathbf{q} = \mathcal{S}\mathbf{h}$ ($\mathbf{h} \in L^2(\Omega)$): one has from (18) that $\mathbf{q} \in H^2(\Omega) \cap H^1_0$.

Using again the Sobolev Embedding Theorem, Theorem 3, one has

$$H^2(\Omega) \hookrightarrow W^{1,s'}(\Omega) \quad \text{if } s' \in \left[1, \frac{2n}{n-2}\right] \Leftrightarrow s \geq \frac{2n}{n+2}.$$

Collecting the latter results together, the following equation is thus well defined granted that $s \in \left[\frac{2n}{n+2}, \frac{n}{n-1}\right)$:

$$\int_\Omega \nabla \mathbf{p} \cdot \mathbb{C}[\nabla \mathcal{S}\mathbf{h}] = \int_\Omega \mathbf{h} \cdot \mathbf{p}.$$

We observe that the equality above follows from the definition of $\mathcal{S}$ (as in the forward problem (17)) and the symmetry of $\mathbb{C}$ (see Eq. (4)).

2.2.3. Characterization of the optimal control

The optimal control $\mathbf{f}$ satisfies, as stated in (12), $\mathbf{f} = -\frac{1}{\varepsilon}\mathcal{P}\mathbf{p}$. We now wish to characterize the projection operator $\mathcal{P} : \mathsf{F} \to \mathsf{F}_{\mathrm{adm}} \subset \mathsf{F}$. Eq. (12) here takes the following meaning:

$$(\varepsilon \mathbf{f} + \mathbf{p}|\mathbf{h})_{L^2(\Omega)} = 0, \quad \forall \mathbf{h} \in \mathsf{F}_{\mathrm{adm}}. \tag{21}$$

Since any test function $\mathbf{h}$ is equal to zero in measure on $\Omega \setminus \Omega_c$, Eq. (21) reduces to

$$\varepsilon(\mathbf{f}|\mathbf{h})_{L^2(\Omega_c)} + (\mathbf{p}|\mathbf{h})_{L^2(\Omega_c)} = 0, \quad \forall \mathbf{h} \in \mathsf{F}_{\mathrm{adm}c}, \tag{22}$$

where $\mathsf{F}_{\mathrm{adm}c} := \{L^2(\Omega_c) | \int_{\Omega_c} \mathbf{f} = 0, \int_{\Omega_c} \mathbf{r} \times \mathbf{f} = 0\}$.

Then $\mathbf{f} = -\frac{1}{\varepsilon}\chi_c \mathbf{p} + \mathbf{f}^\perp$, where $\mathbf{f}^\perp \in \mathsf{F}_{\mathrm{adm}c}^\perp$ and χ_c is the characteristic function of Ω_c. To determine $\mathbf{f}^\perp$ we note that (from the theorem on the dimension of the range and kernel [21]):

Theorem 15. *Let us have $\mathcal{H} \in \mathrm{Lin}(\mathsf{Y}, \mathbb{R}^n)$, Y a (possibly infinite dimensional) Hilbert space, and $n \in \mathbb{N}$. Then $\dim(\ker \mathcal{H})^\perp \leq n$.*

In $\mathbb{R}^2$, if we set $\mathcal{H} = \left[\mathbf{f} \in L^2(\Omega_c) \mapsto \left(\int_{\Omega_c} \mathbf{f}, \int_{\Omega_c} \mathbf{r} \times \mathbf{f}\right) \in \mathbb{R}^3\right]$, then we have $\dim \mathsf{F}_{\mathrm{adm}c}^\perp \leq 3$. Moreover one can readily find a three-dimensional basis, say $\{\mathbf{e}_i\}_{i=1}^3$, for this space. Set $\{\mathbf{e}_1, \mathbf{e}_2\}$ as two constant, linearly independent mappings. Obviously, if $\mathbf{h} \in \mathsf{F}_{\mathrm{adm}c}$,

$$(\mathbf{e}_i|\mathbf{h})_{L^2(\Omega_c)} = \int_{\Omega_c} \mathbf{e}_i \cdot \mathbf{h} = \mathbf{e}_i \cdot \int_{\Omega_c} \mathbf{h} = 0,$$

[5] $W_0^{1,s}(\Omega)$ is the subspace of $W^{1,s}(\Omega)$ consisting of functions having zero trace on $\partial\Omega$; see [11,10].

for $i = 1, 2$. Evidently $\{\mathbf{e}_1, \mathbf{e}_2\} \subset \mathsf{F}_{\mathrm{adm}_c}{}^{\perp}$. Next, let $\mathbf{J} \in \mathsf{Skw}(\mathbb{R}^2) \cap \mathsf{Ort}(\mathbb{R}^2)$ be the chosen perpendicular turn in $\mathbb{R}^2$, as in footnote 4 (the same calculation in $\mathbb{R}^3$ would require a slightly different technique). Choose $\mathbf{e}_3(\mathbf{x}) = \mathbf{J}\mathbf{x}$; then,

$$(\mathbf{e}_3|\mathbf{h})_{L^2(\Omega_c)} = (\mathbf{J}\mathbf{r}|\mathbf{h})_{L^2(\Omega_c)} = \int_{\Omega_c} \mathbf{J}\mathbf{r} \cdot \mathbf{h} = \int_{\Omega_c} \mathbf{r} \times \mathbf{h} = 0.$$

Eventually, given $\{\mathbf{e}_i\}_{i=1}^3$ as above, $\mathbf{f} \in \mathsf{F}_{\mathrm{adm}}$ turns out to be

$$\mathbf{f} = -\frac{1}{\varepsilon}\chi_c \mathbf{p} + \sum_{i=1}^{3} l_i \mathbf{e}_i, \tag{23}$$

where the $(l_i)_{i=1}^3 \in \mathbb{R}^3$ are the Lagrangian multipliers associated with the constraint of null net force and torque (see the definition of $\mathsf{F}_{\mathrm{adm}_c}$ above) and so they are unknowns of the problems.

2.3. The system of equations

Here below we summarize the results of the present section, pointing out the system of differential equations, in weak form, that one may want to solve in practice:

$$\text{find } \mathbf{u} \in H^2(\Omega) \cap H^1_0(\Omega),\ \mathbf{p} \in W_0^{1,s}(\Omega),\ (l_i)_{i=1}^3 \in \mathbb{R}^3,\ s \in \left[\frac{2n}{n+2}, \frac{n}{n-1}\right)$$

$$\text{such that } \forall \mathbf{q} \in W_0^{1,s'}(\Omega),\ \forall \mathbf{v} \in H_0^1(\Omega):$$

$$\begin{cases} \displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{u} \cdot \nabla\mathbf{v} + \int_\Omega \mathbf{f} \cdot \mathbf{v} = 0, \\ \displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{p} \cdot \nabla\mathbf{q} + \sum_{j=1}^{N} \delta_{\mathbf{x}_j}\mathbf{u} \cdot \delta_{\mathbf{x}_j}\mathbf{q} = \sum_{j=1}^{N} u_{0_j} \cdot \delta_{\mathbf{x}_j}\mathbf{q}, \\ \displaystyle\mathbf{f} + \frac{1}{\varepsilon}\mathbf{p} - \sum_{i=1}^{3} l_i \mathbf{e}_i = 0, \\ \displaystyle\int_\Omega \mathbf{f} = 0, \\ \displaystyle\int_\Omega \mathbf{r} \times \mathbf{f} = 0. \end{cases} \tag{24}$$

3. Boundary control with Neumann or mixed conditions

While traction force microscopy on flat surfaces is nowadays a well established technique for cells moving on flat surfaces, the challenging goal is currently to obtain a good reconstruction of the stress exerted by a cell in its physiological three-dimensional migration environment. In a typical experimental setup, a cell is immersed in a Matrigel box as in Fig. 1 and exerts a stress on the inner boundary of the gel; the traction at the inner surface plays here the role of the unknown of the problem. Homogeneous Dirichlet or Neumann condition can be considered for the outer boundary, i.e. the walls of the box.

3.1. The forward problem

Let $\Omega \subset \mathbb{R}^3$ be an open bounded domain with C^2-regular border, as in Fig. 1. The boundary conditions characterize a mixed problem in linear elasticity and, in this section, we consider $\mathsf{U} = H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$, $\mathsf{F} = H^{\frac{1}{2}}(\Gamma_N)$, $\mathbf{c} := \mathbf{f}$ and $\mathbf{b} = 0$. The forward problem (1) or (5) now reads:

$$\text{given } \mathbf{f} \in H^{\frac{1}{2}}(\Gamma_N),\ \text{find } \mathbf{u} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega) \text{ such that for all } \mathbf{v} \in H^1_{0,\Gamma_D}(\Omega):$$

$$\int_\Omega \nabla\mathbf{u} \cdot \mathbb{C}[\nabla\mathbf{v}] = \int_{\Gamma_N} \mathbf{f} \cdot \mathbf{v}. \tag{25}$$

The above problem admits a unique solution in $H^1(\Omega)$ thanks to the Lax–Milgram Lemma (Theorem 4). If we consider the setup as in Fig. 1, where $\Gamma_D \neq \emptyset$ and $\mathrm{cl}(\Gamma_N \cup \Gamma_D) = \emptyset$, we can apply Theorem 5 to obtain the estimate

$$\|\mathcal{S}\mathbf{f}\|_{H^2(\Omega)} \le k\|\mathbf{f}\|_{H^{\frac{1}{2}}(\Gamma_N)}, \quad k > 0, \tag{26}$$

where $\mathcal{S}\mathbf{f} = \mathbf{u}$ iff (25) is satisfied. For a pure Neumann problem ($\Gamma_N = \partial\Omega$), the same results hold, but the solution $\mathbf{u}$ is unique up to a rigid motion (see [14]).

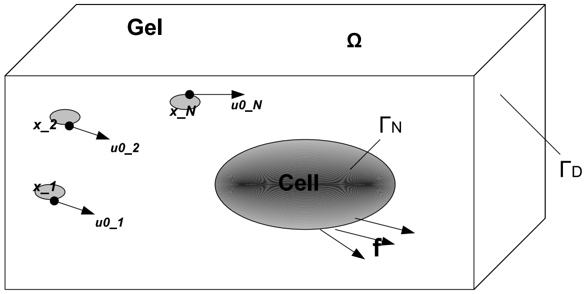

Fig. 1. Three-dimensional setup.

3.1.1. The admissible force space

As in the case of distributed control of the previous section, since neither a force nor a constraint acts on the cell, we define the admissible force space as

$$\mathsf{F}_{\text{adm}} := \left\{ \mathbf{g} \in \mathsf{F} = H^{\frac{1}{2}}(\Gamma_N) \,\middle|\, \int_{\Gamma_N} \mathbf{f} = 0,\ \int_{\Gamma_N} \mathbf{r} \times \mathbf{f} = 0 \right\}. \tag{27}$$

This is a closed subspace of $L^2(\Gamma_N)$ and therefore also of $\mathsf{F} = H^{\frac{1}{2}}(\Gamma_N)$ since $H^{\frac{1}{2}}(\Gamma_N) \hookrightarrow L^2(\Gamma_N)$, the proof being the same as the one given in the previous section (it is sufficient to exchange Ω with Γ_N, noting also that Γ_N has finite measure).

3.2. Optimal control

3.2.1. The penalty functional

We search for $\mathbf{f} \in \mathsf{F}_{\text{adm}}$ which minimizes the functional in (8). The discussion below is very similar to the one in the previous section and some details are omitted.

We have proved in (26) that the choice of U, F made in this section provides a continuous solution operator $\mathcal{S}$. Since the solution $\mathbf{u}$ belongs to $H^2(\Omega)$, the observation map $\mathcal{O}$ is also continuous. In fact, by the Sobolev Embedding Theorem, Theorem 3, $H^2(\Omega) \hookrightarrow C^0(\text{cl}\ \Omega)$ when $n = 2, 3$ and, thanks to Proposition 7, (7) is clearly satisfied. We can then apply Theorem 12 to see that in this case our functional $\mathcal{J}$ admits a unique minimum point and it is differentiable therein.

3.2.2. The adjoint state

In the following, we explicitly characterize the operator $\mathcal{A}$ that appears in (11) and prove some of its properties. In this case, $\mathcal{A} \neq \mathcal{S}^{-1}$; in fact we state the following counterpart of (11) (cf. [9]):

$$\text{find } \mathbf{p} \in W^{1,s}_{0,\Gamma_D}(\Omega) \text{ s.t. } \forall \mathbf{q} \in W^{1,s'}_{0,\Gamma_D}(\Omega):$$

$$\int_\Omega \nabla\mathbf{p} \cdot \mathbb{C}[\nabla\mathbf{q}] = (\mathcal{O}\mathbf{u} - u_0) \circ \mathcal{O}\mathbf{q}. \tag{28}$$

We now state the well posedness of the above equation, the proof being identical to that of Proposition 14.

Proposition 16. *The problem in (28) is well posed when $s \in [1, \frac{n}{n-1})$, s' is conjugate to s, Ω is a bounded domain with C^2-boundary and $n \le 3$.*

It happens that $\mathbf{p} \in L^s(\Gamma_N)$ because from Trace Theorem 2,

$$W^{1,s}(\Omega) \hookrightarrow L^s(\partial\Omega) \quad \text{if } s < n.$$

Moreover, let $\mathbf{q} = \mathcal{S}\mathbf{h}$ ($\mathbf{h} \in H^{\frac{1}{2}}(\Gamma_N)$); one has, according to (18), that $\mathbf{q} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega)$.

Using again the Sobolev Embedding Theorem, Theorem 3, we find that

$$H^2(\Omega) \hookrightarrow W^{1,s'}(\Omega) \quad \text{if } s' \in \left[1, \frac{2n}{n-2}\right] \Leftrightarrow s \ge \frac{2n}{n+2}.$$

By virtue of Trace Theorem 2, one has $H^1(\Omega) \hookrightarrow H^{\frac{1}{2}}(\Gamma_N)$; then it is worth pointing out the following embedding:

$$H^1(\Omega) \hookrightarrow L^{s'}(\partial\Omega) \quad \text{if } s' \in \left[1, \frac{2n-2}{n-2}\right] \Leftrightarrow s \ge \frac{2n-2}{n}$$

that guarantees $\mathbf{h} \in L^{s'}(\partial\Omega)$.

According to the results above, the following equation is thus well defined, granted that $s \in [\frac{2n-2}{n}, \frac{n}{n-1}]$:

$$\int_\Omega \nabla \mathbf{p} \cdot \mathbb{C}[\nabla \mathcal{S}\mathbf{h}] = \int_{\Gamma_N} \tau_{\Gamma_N} \mathbf{p} \cdot \mathbf{h}. \tag{29}$$

We observe that the equality above follows from the definition of $\mathcal{S}$ (as in the forward problem (25)) and the symmetry of $\mathbb{C}$ (see Eq. (4)).

Remark 17. Similar arguments hold for a pure Neumann problem, except for minor details.

Remark 18. A proof of the well posedness for a pure Neumann problem when $\mathrm{supp}\ \mathcal{O} \subset \partial\Omega$ is given in [22] using the potential theory (suitable for the boundary elements numerical method). Here we do not constrain the support of the observation operator.

3.2.3. Characterization of the optimal control

The optimal $\mathbf{f}$, as stated in (12), satisfies $\mathbf{f} = -\frac{1}{\varepsilon}\mathcal{P}\mathcal{S}^T\mathcal{A}\mathbf{p}$. It can be useful to recall that Eq. (12) here takes the following meaning (see (29)):

$$\varepsilon(\mathbf{f}|\mathbf{h})_{H^{\frac{1}{2}}(\Gamma_N)} + \int_{\Gamma_N} \mathbf{p} \cdot \mathbf{h} = 0, \quad \forall \mathbf{h} \in \mathsf{F}_{\mathrm{adm}}. \tag{30}$$

Given $\mathbf{p} \in W^{1,s}(\Omega)$, thanks to the Riesz Theorem (see [12]), a unique solution $\mathbf{f} \in H^{\frac{1}{2}}(\Gamma_N)$ of this problem exists since $\mathbf{h} \in H^{\frac{1}{2}}(\Gamma_N) \mapsto \int_{\Gamma_N} \mathbf{p}\cdot\mathbf{h}$ is a linear and continuous functional on $H^{\frac{1}{2}}(\Gamma_N)$. Unfortunately, Eq. (30) cannot be approximated by using standard FEM tools, even when $\mathsf{F}_{\mathrm{adm}} = \mathsf{F}$, since they usually do not deal with non-integer Sobolev spaces. A reasonable and computationally cheap way to overcome these difficulties is addressed in the next part.

3.2.4. A hypothesis for the observation operator and consequences

We note that, according to Theorem 2, the trace of an element of $W^{1,s}(\Omega)$ (s as before) does not necessarily belong to $H^{\frac{1}{2}}(\Gamma_N)$. Nevertheless, if we add an additional hypothesis, we can achieve more regularity for the adjoint state.

Hypothesis 19. The support of the observation operator $\mathcal{O}$ is an open set contained in Ω' which is such that $\mathrm{cl}\ \Omega' \subsetneq \Omega$.

Using Hypothesis 19, we are able to state (see [23] for the proof):

Proposition 20. *Let $\Omega'' \subset \Omega \setminus \Omega'$, strictly. Then $\mathbf{p}|_{\Omega''}$ belongs to $H^1(\Omega'')$.*

Since, by Hypothesis 19 above, $\mathrm{dist}(\Gamma_N, \Omega') > 0$, we can certainly choose a set $\Omega'' \subset \Omega \setminus \Omega'$ such that $\Gamma_N \subset \Omega''$. Then, by (20), $\mathbf{p}|_{\Omega''}$ belongs to $H^1(\Omega'')$ and, by the trace Theorem 2, $\tau_{\Gamma_N}\mathbf{p}$ belongs to $H^{\frac{1}{2}}(\Gamma_N)$. According to [9], the adjoint variable $\mathbf{p}$, the solution of (28), actually solves

$$\int_\Omega \mathbf{p} \cdot (\nabla \cdot (\mathbb{C}\nabla \mathbf{q})) + (\mathbf{p}|(\mathbb{C}\nabla\mathbf{q})\mathbf{n})_{H^{\frac{1}{2}}(\Gamma_N)} = (\mathcal{O}\mathbf{u} - u_0) \circ \mathcal{O}\mathbf{q}. \tag{31}$$

If we put the last equation inside Eq. (12) with $\mathbf{q} = \mathcal{S}\mathbf{h}$ ($\mathbf{h}$ is any function in $H^{\frac{1}{2}}(\Gamma_N)$, as before), we find that

$$\mathbf{f} = -\frac{1}{\varepsilon}\mathcal{P}\mathbf{p},$$

which is a purely algebraic equation in the non-constrained case (i.e., when $\mathcal{P}$ is the identity). The constrained case can be treated as above, as we shall see in the next part. Before going on, we shall note that, thanks to Hypothesis 19, the problem is well posed on choosing $\mathsf{F} = L^2(\Gamma_N)$.

3.2.5. The space $\mathsf{F}_{\mathrm{adm}}{}^{\perp}$

In the constrained case the latter equation can be exploited as in Section 2, and

$$\mathbf{f} = -\frac{1}{\varepsilon}\tau\mathbf{p} + \mathbf{f}^{\perp}$$

with $\mathbf{f}^{\perp} \in \mathsf{F}_{\mathrm{adm}}{}^{\perp}$. As said before, we consider $\mathsf{F}_{\mathrm{adm}}$ as in the definition (27) but with $\mathsf{F} = L^2(\Gamma_N)$. The actual calculation of a basis for its orthogonal $\mathsf{F}_{\mathrm{adm}}{}^{\perp}$ can be performed in the same way as in Section 2 (there is a slight difference due to the fact that we are working in three dimensions). Actually, by the theorem of the range and kernel (Theorem 15 of Section 2) we argue that $\dim(\mathsf{F}_{\mathrm{adm}}{}^{\perp}) \leq 6$, since we are now in $\mathbb{R}^3$. But one can readily find a six-dimensional basis for $\mathsf{F}_{\mathrm{adm}}{}^{\perp}$ letting $(\mathbf{e}_i)_{i=1}^3$ be three constant and linearly independent mappings and $\mathbf{e}_{i+3} = \mathbf{r} \times \mathbf{e}_i,\ i = 1, 2, 3$. The conclusion of the proof follows exactly the same calculations and reasoning as the discussions on the analogous problem faced in Section 2.

Another observation that is worth making is the following: the null total moment of the force constraint can be a little tricky to implement. For this reason, and only in this paragraph, we deal with the following admissible force space:

$$\mathsf{F}_{\text{adm}} := \left\{ \mathbf{g} \in \mathsf{F} = L^2(\Gamma_N) \middle| \int_{\Gamma_N} \mathbf{f} = 0 \right\}.$$

Loosely speaking, we do not enforce the equilibrium of the momentum and we just constrain the force field to have null resultant. This choice of F_{adm}, as the reader may easily verify, does not affect the well posedness results found previously. In such a case, we find that the set of equations (where $(l_i)_{i=1}^3$ is the set of Lagrangian multipliers associated with the constraint)

$$\mathbf{f} = -\frac{1}{\varepsilon}\tau\mathbf{p} + \sum_{i=1}^{3} l_i \mathbf{e}_i$$

$$\int_{\Gamma_N} \mathbf{f} = 0$$

can be solved explicitly thanks to the fact that the basis mappings $(\mathbf{e}_i)_{i=1}^3$ assume constant values. The above equation is thus equivalent to

$$\mathbf{f} = \frac{1}{\varepsilon}\left(\frac{1}{|\Gamma_N|}\int_{\Gamma_N} \tau\mathbf{p} - \tau\mathbf{p}\right)$$

where $|\Gamma_N|$ the $(n-1)$-measure of Γ_N. Of course, this kind of reasoning can be repeated when treating the problem discussed in Section 2.

3.2.6. The system of equations

Here below we summarize the results of this section, pointing out the system of differential equations in weak form that one may want to solve in practice. Here we consider the assumption made in Section 3.2.5, i.e. we only consider the null total force constraint, which gives us a considerably simpler set of equations:

$$\text{find } \mathbf{u} \in H^1_{0,\Gamma_D}(\Omega) \cap H^2(\Omega),\ \mathbf{p} \in W^{1,s}_{0,\Gamma_D}(\Omega),\ s \in \left[\frac{2n-2}{n}, \frac{n}{n-1}\right]$$

$$\text{such that } \forall\mathbf{q} \in W^{1,s'}_{0,\Gamma_D}(\Omega),\ \forall\mathbf{v} \in H^1_{0,\Gamma_D}(\Omega):$$

$$\begin{cases} \displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{u}\cdot\nabla\mathbf{v} + \int_{\Gamma_N} \mathbf{f}\cdot\mathbf{v} = 0, \\ \displaystyle\int_\Omega \mathbb{C}\nabla\mathbf{p}\cdot\nabla\mathbf{q} + \sum_{j=1}^N \delta_{\mathbf{x}_j}\mathbf{u}\cdot\delta_{\mathbf{x}_j}\mathbf{q} = \sum_{j=1}^N u_{0_j}\cdot\delta_{\mathbf{x}_j}\mathbf{q}, \\ \displaystyle\mathbf{f} = \frac{1}{\varepsilon}\left(\frac{1}{|\Gamma_N|}\int_{\Gamma_N} \tau\mathbf{p} - \tau\mathbf{p}\right), \end{cases} \tag{32}$$

We are now in the position to step back to the original biological problem and recover the physical interpretation of Eqs. (32). This reinterpretation may become more apparent on assuming that the elastic gel is isotropic, and so the elasticity tensor takes a particularly simple form, depending on just two material parameters (μ and λ, the usual Lamé moduli). In this case, Eqs. (32) are rewritten as

$$\begin{cases} \displaystyle\int_\Omega (\mu\nabla\mathbf{u}\cdot\nabla\mathbf{v} + \lambda(\nabla\cdot\mathbf{u})(\nabla\cdot\mathbf{v})) - \frac{1}{\varepsilon}\left(\int_{\Gamma_N} \mathbf{p}\cdot\mathbf{v} + \frac{1}{|\Gamma_N|}\int_{\Gamma_N}\mathbf{p}\cdot\int_{\Gamma_N}\mathbf{v}\right) = 0, \\ \displaystyle\int_\Omega (\mu\nabla\mathbf{p}\cdot\nabla\mathbf{q} + \lambda(\nabla\cdot\mathbf{p})(\nabla\cdot\mathbf{q})) + \sum_{j=1}^N \delta_{\mathbf{x}_j}\mathbf{u}\cdot\delta_{\mathbf{x}_j}\mathbf{q} = \sum_{j=1}^N u_{0_j}\cdot\delta_{\mathbf{x}_j}\mathbf{q}. \end{cases} \tag{33}$$

The differential system in weak form (33) finally answers the following question. Given an isotropic elastic material (like polyacrylamide), with known elastic moduli λ and μ, deformed by a living cell embedded in it, we have experimentally measured pointwise displacements $\mathbf{u}$ in the positions $\mathbf{x}_j$. The force field that produces such a displacement, in the sense of the one minimizing the penalty functional (8), is the traction field $\mathbf{f}$, the solution of the system (33), defined on the boundary Γ_N where the gel and the cell are in contact. The traction $\mathbf{f}$ is simply proportional to the solution of the adjoint equation $\mathbf{p}$, up to a correction due to the constraint of a null average. The two differential equations are coupled by linear non-differential terms, of surface or volumetric type. In this respect, one can say pictorially that the discrepancy between the measured and calculated displacements (the right hand side of Eq. (33)(b)) is the volumetric source for the adjoint field $\mathbf{p}$, its value at the interface being basically the cell traction that we are looking for.

3.2.7. An analytical example

The following example with reduced complexity in idealized geometry allows to estimate quantitatively the efficacy of the inversion method. Consider a spherical cell of radius r_1 immersed in an infinite elastic medium with observed displacement u_2 at every point of a spherical surface located in $r = r_2$. The symmetry of the problem allows one to rewrite the system of Eqs. (33) in strong form as follows:

$$\mu\left(\frac{1}{r^2}\left(r^2u\right)'\right)' = 0, \qquad \mu u'(r_1) = -p(r_1)/\epsilon \tag{34}$$

$$\mu\left(\frac{1}{r^2}\left(r^2p\right)'\right)' = \delta_{r_2}(u(r) - u_2), \qquad p'(r_1) = 0, \qquad p(+\infty) = 0 \tag{35}$$

where $u(r)$ is the radial component of the displacement, which depends only on the radial coordinate, and the prime $'$ denotes differentiation with respect to r. Notice that the condition of null resultant force does not explicitly appear, as it is automatically satisfied in a radially symmetric problem.

The fundamental solution for the elasticity operator in spherical coordinates applies where the solution is known to be regular:

$$p(r) = ar + \frac{b}{r^2} \quad \text{in } [r_1, r_2), \tag{36}$$

$$p(r) = cr + \frac{d}{r^2} \quad \text{in } (r_2, +\infty). \tag{37}$$

The boundary conditions listed in Eqs. (34) and (35) fix two integration constants:

$$p'(r_1) = a - 2\frac{b}{r_1^3} = 0 \Rightarrow a = 2\frac{b}{r_1^3} \tag{38}$$

$$p(+\infty) = 0 \Rightarrow c = 0 \tag{39}$$

and so

$$p(r) = b\left(\frac{2r}{r_1^3} + \frac{1}{r^2}\right) \quad \text{in } [r_1, r_2), \tag{40}$$

$$p(r) = \frac{d}{r^2} \quad \text{in } (r_2, +\infty). \tag{41}$$

The remaining integration constants are fixed by the continuity of the displacement and the traction jump in r_2:

$$p(r_2^-) = p(r_2^+) \tag{42}$$

$$\mu p'(r_2^+) - \mu p'(r_2^-) = u(r_2) - u_2. \tag{43}$$

Elementary calculations yield, in particular,

$$b = -\frac{r_1^3}{6\mu}\left(u(r_2) - u_2\right) \tag{44}$$

so the value of the adjoint field p in r_1 takes the value

$$p(r_1) = -\frac{r_1}{2\mu}\left(u(r_2) - u_2\right). \tag{45}$$

The solution of the force balance equation (34) is, again, the fundamental solution where the integration constants are fixed by the boundary conditions that can now be expressed, thanks Eq. (45), in terms of u itself:

$$u(r) = -\frac{1}{4\mu^2\epsilon}\left(u(r_2) - u_2\right)\frac{r_1^4}{r^2} \tag{46}$$

which is an implicit expression for the displacement $u(r)$ depending on its own value in r_2. It is particularly useful to evaluate the expression (46) at such a point, obtaining

$$u(r_2) = u_2\left(1 + 4\epsilon\mu^2\frac{\rho^2}{r_1^2}\right)^{-1}. \tag{47}$$

The expression (47) indicates the role of the stabilization parameter ϵ and that of the geometric ratio ρ in the inversion procedure. The inverted datum is always damped with respect to the measured one. Assuming that u_2 is exactly known, as expected the exact datum is recovered as $\epsilon \to 0$. For fixed ϵ, we obtain the minimum error in the inversion for $\rho = \frac{r_2}{r_1} \to 1$, that is when the two surfaces approach each other.

The specific interest of the inversion procedure is however in deducing the traction forces at the surface, namely $f = -p(r_1)/\epsilon$. In this idealized (well posed) system it is possible to evaluate the error produced by the inversion algorithm in the reconstruction of a known force field: we can exactly recover the true force $\tilde{f}$ that produces the displacement u_2 in r_2 and compare with the inverted one.

The solution of the "true" elasticity problem will be

$$\tilde{u}(r) = \frac{b}{r^2} \tag{48}$$

where the load at the boundary is provided by the "true" force $\tilde{f}$:

$$\mu \tilde{u}'(r_1) = \tilde{f}. \tag{49}$$

The requirement that the solution matches the "true" value u_2 in r_2 fixes the relationship between the applied force and the observed displacement:

$$\tilde{f} = -2\mu u_2 \frac{r_2^2}{r_1^3}. \tag{50}$$

On the other hand, the inverted traction f is provided by Eqs. (45) and (47),

$$f = -p(r_1)/\epsilon = \frac{r_1}{2\mu\epsilon}\,(u(r_2) - u_2) \tag{51}$$

and so

$$f = \tilde{f}\left(1 + 4\epsilon\mu^2 \frac{\rho^2}{r_1^2}\right)^{-1}. \tag{52}$$

The relation (52), fully analogous to (47), indicates the role of the mutual distance between the traction surface and the location of the measured data in this boundary control problem.

Final remarks

An inverse problem inspired by biophysical practice has been addressed in terms of formal and rigorous statements. The specific characteristic of this problem is the assumption of pointwise observations: they call for a generalization of the classical elasticity theory to forcing terms (for the adjoint problem) that are Borel measures.

Our main aim here is the correct statement of the set of equations that can be adopted to address traction force microscopy in a three-dimensional environment, a challenging question in cell biology. The mathematical theory largely stands on known results, while the novelty of this contribution lies in the specific form of the system of equations (32) and their well posedness for the application at hand. Now, on this basis, the reader interested in biological applications can go forward to the numerical approximation of these two elliptic partial differential equations, coupled by the boundary conditions. The integration of the reduced symmetric problem of Section 3.2.7 provides a concrete example of the method that can be helpful in view of its numerical integration and application to real data.

It may be worth recalling that force traction microscopy in three dimensions is still in its infancy; just in very recent years have imaging techniques revealed detail of the patterns of the mechanical strain produced by cells in their movement. Early attempts at quantitative inversion have been carried out [24], but a precise analysis of the methods seems to be still lacking. The content of this paper now provides the basis for a mathematically precise application of the inversion method to real biophysical questions.

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